20 June 1955

Mr. Richard Morgan
2748 Sixth Avenue
Sacramento, California

Dear Richard:

I have been thinking about the matter that we discussed on your last trip here - the question of our collaborating with your department in an attack on mental disease.

I think that it would be possible to formulate a program that would be of interest to you and would also fit in satisfactorily with our facilities and interests. The proposal is that we would carry on some fundamental studies related to the possibility that some mental diseases are molecular diseases.

You know about the discovery of molecular diseases - our work on sickle cell anemia, published in 1949, and the more recent developments. I enclose two copies each of our first paper and a review article, my Harvey Lecture, given last year. The history of molecular diseases is that, although all hereditary diseases may be called molecular diseases, in that it is likely that genes are molecules, and hereditary diseases may be ascribed to abnormalities of genes, and possibly to abnormalities of other molecules manufactured under the guidance of genes, sickle cell anemia was in fact the first disease shown clearly to be caused by abnormal molecules, present in the bodies of patients in place of normal adult human hemoglobin molecules. In the Harvey Lecture mention is made of other diseases, due to the abnormal hemoglobins C, D, and E, which were discovered after the work on sickle-cell-anemia hemoglobin. During the past year several more abnormal hemoglobins have been discovered.

In 1934 it was found by Fölling that a considerable number of individuals showing idiocy, or imbelicity, or occasionally feeble-mindedness, excrete large amounts of phenylpyruvic acid in their urine. This biochemical abnormality, which seems clearly to be the cause of the mental deficiency, is presumably the result of the inability of the individual to carry out the oxidation of phenylalanine to tyrosine. I think that it would be worth while, in order to verify this as a molecular disease, which it presumably is, to attempt to isolate a protein similar to but somewhat different from a protein normally present, which is involved in this oxidation - that is, one of the enzymes. If this protein could be isolated, its investigation might provide valuable information about the nature of the disease. It is, of course, not to be expected that a study of this sort would lead immediately to a therapy for the disease - we would be interested primarily in obtaining basic information about the nature of mental disease, which would later be useful in the effort to develop new therapeutic methods.

I may say that there is some evidence that the enzymes involved are in the liver and not in the bloodstream. Presumably our investigation along these lines would have to begin with the study of the enzyme-catalyzed oxidation of phenylalanine, probably with beef liver as the starting material, and only later would human enzyme be studied.

A second part of our proposal might be the search for other biochemical abnormalities in mental patients. This part has, I think, significant possibilities, but it would, of course, be a big job. I think that it would begin with the study of samples of blood and urine. It is impossible to make an exhaustive study of this sort, because of the labor involved; we would try to move in the directions that seemed to us to offer the greatest chance of leading to a significant discovery.

I should not want to embark on a program of this sort unless there were funds available for support of more than one full-time research man (perhaps two or three) and for the equipment necessary for the work, and also, over a continued period of time. I would look on the job as a 14-year job - that is, as extending until my retirement, in 1969, and I probably would not want to embark upon it unless there was definite indication of support over at least a 5-year period.

Please let me know if you want any more information - more copies of these reprints or of others of our papers, for example. I shall look forward to having a conference with you and other members of your department later on.

Sincerely yours,

Linus Pauling:W
Encls.